37. (Amended) A method for the *ex vivo* engineering of mineralized collagenous matrix, the method comprising the steps of:

providing an artificial stabilized composition having a globular surface morphology of loosely interconnected rounded granules with interconnected micropores,

applying a suspension of osteoblasts in physiological media on the composition,

incubating the mineralized collagenous bone matrix secreted [selected] by the osteoblasts from the culture; and

implanting the isolated collagenous bone matrix in a patient.

REMARKS

This is in response to the Official Action mailed July 13, 2000 in the above-referenced application. Claims 1-3, 5, 6, 10-15, 19-35 and 37 are before the Examiner. Applicants note with appreciation the indication by the Examiner that Claim 20 would be allowable if rewritten in independent form and that claims 10 and 37 are allowed. Claims 1, 3, 5, 6, 13, 15, 20, 24, 25, 35 and 37 are amended as discussed in more detail below. Applicants note that Claim 37 is amended merely to correct a typographical error. The remaining claims are amended to remove all reference to "films." Claims 4, 7-9, 16-18 and 36 are cancelled without prejudice or disclaimer to Applicants. The issues raised in the Official Action are addressed below in the order set forth therein.

Objections to the Specification

The Office Action objects to the present application as not containing an abstract of the disclosure as required by 37 CFR 1.72(b). An Abstract was attached with Applicants' prior response but was apparently inadvertently separated from the response. Accordingly, attached herewith please find an abstract in accordance with 37 CFR 1.72(b). In view of the foregoing, Applicants respectfully request withdrawal of the objections to the specification

Claim Rejections under 35 USC § 102

Claims 1-3, 5-8, 11-18, 21-23, 31 and 33-36 are rejected under 35 USC §§102(a) or (b) as being anticipated by Davies (WO 94/26872). Applicants note that the cancellation of claims 7,

8, 16, 17 and 18 has rendered the rejection of these claims *moot*. Applicants respectfully disagree with the Examiner with respect to both the §§102(a) and/or (b) rejection and submit that the Davies reference does not anticipate the noted claims. The Examiner asserts that Davies discloses a sintered hydroxyapatite film in a manner similar to the present invention due to the silica of quartz permeating into the sol during sintering. In this regard, the Davies reference is directed to a calcium phosphate based thin film for culturing bone cells thereon. The Davies publication does not specify the make up of the thin film therein, other than to note that the thin film comprises both calcium hydroxyapatite and tricalcium phosphate in different ratios. Indeed, as the Office acknowledges, Davies is completely silent as to the provision of stabilized calcium phosphate phases and more specifically, stabilized tricalcium phosphate.

Davies only teaches making a thin film that is always provided on a quartz substrate. Davies does not teach or suggest making a composition that is purposely stabilized by doping with stabilizing entities as recited in independent Claims 1 and 13. Further, Davies does not teach such a composition that can be made in different formats, for example, as powders, bulk three dimensional pieces or thick coatings, as recited in Claims 3 and 14. Still further, Davies does not teach or suggest adding the stabilizing entities in solution to the hydroxyapatite substance before sintering, as recited in Claims 6 and 19.

The method and thin film as taught by Davies is entirely dependent on the provision of a substrate on which the thin film is made and always supported thereon. Davies always refers to the "substrate" for providing support for the thin film and which can allow for certain analytical assessment of the film after the culture of the cells. Davies nowhere teaches or suggests any chemical effect a quartz substrate may have, if any, on the thin film. Its sole contemplated use is to provide a suitable physical substrate that could be sintered and could be used in analytical testing. This is also further supported by the fact that Davies teaches the use of other materials such as metals, polymers or ceramics as a support.

Davies does not teach anything more than a thin analytical film. Davies certainly does not teach or suggest the composition as presently claimed that is formed by the actual doping of the hydroxyapatite prior to its sintering, much less without a supporting substrate. Indeed, in the circumstance of no substrate, where, for example, a quartz substrate is not present, Davies

nowhere identifies a separate and additional use of a substituting element as necessary. This further illustrates that Davies does not teach any chemical function of quartz in the compositions or the method of the present invention.

As discussed *supra*, Davies teaches making a thin film supported on a substrate. Davies does not teach or suggest a composition or method for making any three-dimensional structure or implants because Davies does not realize or teach the effect of stabilization by doping of the hydroxyapaptite material. This is especially true since the present method for processing bulk three-dimensional pieces or implants does not involve the use of a substrate that provides any stabilizing entities. Davies does not teach or suggest the need for deliberate doping of stabilizing entities. In contrast, in the presently claimed invention there is a specific requirement of mixing in the processing method to make the composition in order to achieve the desired dopant interactions necessary to stabilize the biomaterial compound, especially three-dimensional pieces and implantable devices. Again, since Davies only teaches a thin diagnostic film always supported on a substrate this cannot anticipate the presently claimed composition especially in the form of bulk pieces and implantable devices.

To reiterate, the claimed invention is not inherent and not anticipated by the Davies reference. Davies does not teach each and every element of the noted rejected claims and for this reason cannot anticipate the noted claims. Specifically, Davies does not teach an isolated artificial sintered composition developed by the conversion of a hydroxyapatite substance doped with stabilizing entities at sintering temperatures into insolubilized and stabilized tricalcium phosphate.

For these reasons *supra*, Applicants submit that Davies does not teach the claimed invention, either explicitly or inherently and accordingly request withdrawal of this rejection. Since claims 8, 16, 17 and 18 have been cancelled, the rejection of these claims based on Davies is *moot*.

Claims 1-4, 7, 9, 12-14, 17, 19, 22, 23, 31 and 34 are also rejected under 35 USC § 102(b) as being anticipated by Kasuga et al (U.S. 5,232,878). Again, the Applicants respectfully disagree with the Examiner. The present invention as noted in independent claims 1, 13, and 19 is directed to a bioactive composition which supports bone cell activity. As taught in the present

specification at pages 10, 19 and 22-23, bioactive refers to the ability to support osteoblastic bone growth over and throughout structures substantially or exclusively made of the presently claimed composition and simultaneously promote natural controlled extracellular resorption of the composition by osteoclasts in a process resembling normal bone turnover. Thus the presently claimed composition is useful for applications in which ingrowth of bone matrix and general *in vivo* bone remodeling is desired. This is a unique feature of the presently claimed composition that is not taught by Kasuga.

Kasuga is directed to a process for producing an inorganic biomaterial which has a good strength and biocompatibility such that it can be used as a dental implant or an artificial bone implant. "Biocompatibility" refers to the fact that the material as produced can be used *in vivo* as an implant with little adverse physiological effect. This is not the same as "bioactive" as is recited in the present claims and discussed above. The implant of Kasuga is a physical dispersion of crystallized glass or calcium phosphate within a skeleton of zirconia, which provides for increased mechanical properties. The fact that Kasuga is directed to a "glass"structurally identifies the material as being different to that presently claimed. It is only in the later steps of Kasuga's process that the glass is heated to form a crystallized powder which is then mixed with zirconia or alumina. "Partially stabilized zirconia" refers to zirconia that is prepared to attain high strength and high toughness with respect to stress-induced transformation (column 6, lines 38-44) such that it can be used as a biomaterial for artificial bones and dental implants. Zirconia or alumina is added only to increase the mechanical strength of the glass. There is no bioactivity attributed to these additions.

The Kasuga implant does not support "bone cell activity" leading to bone remodeling as seen *in vivo* as is the case in the presently claimed composition. Kasuga also does not teach converting a hydroxyapatite substance into insolubilized and stabilized tricalcium phosphate having a morphology for supporting bone cell activity as is recited in claims 1 and 13 from which the rejected claims depend. Therefore, Kasuga does not teach or suggest each and every element as is required in the noted claims and for these reasons, this reference cannot anticipate the presently claimed invention. Applicants accordingly request withdrawal of this rejection.

Claims 1-7, 11-14, 17, 21, 23, 24 and 31-34 are also rejected under 35 USC § 102(b) as being anticipated by Kijima et al (U.S. 4,983,182). Again, the Applicants respectfully disagree with the Examiner. Kijima is directed to an interfacial layer on the surface of a zirconia implant. The interfacial layer renders the surface of the implant biologically active such that the implant chemically bonds to vital tissue. "Biologically active" is not the same as "bioactive" as is recited in the present claims. The composition of the interfacial layer is either alpha TCP and zirconia or hydroxyapatite and zirconia as these materials are recognized as being biologically active. However, there is no reference beyond bonding to vital tissue. The present invention enables remodeling where natural cell-based processes involve the implant in a dynamic environment that is in keeping with the body's continual maintenance of the skeleton.

Again, as with Kasuga, "stabilized zirconia" refers to enhanced mechanical stability and strength. Kijima and Kasuga teach physical solid state stabilization rather than stabilization in a biological environment. This is no way refers to biological stability as in the presently claimed invention. Further, Kasuga teaches away from the intimate mixing presently taught as required for the resultant composition to form. Kasuga suggests in column 2, lines 44-53, that a limitation of the addition of zirconia to calcium phosphate is the tendency for the compounds to interact and this compromises the strength and toughness of the ceramic composite material obtained. Thus Kasuga teaches making a completely different composition having different physiological characteristics compared to the presently claimed invention.

Therefore, Kijima does not teach or suggest the composition as presently claimed in claim 1 where the composition has a morphology that supports bone cell activity which includes the promotion of bone cell proliferation and differentiation, deposition of mineralized matrix by osteoblasts and resorption of the composition by osteoclasts and further that the composition comprises insolubilized tricalcium phosphate. Claim 13 contains similar amendments to that of claim 1. Therefore, Kijima does not teach or suggest each and every element as is required in the noted claims and for these reasons, this reference cannot anticipate the presently claimed invention. Applicants request withdrawal of this rejection.

Claim Rejections under 35 USC §103

Claims 4, 9, 24-30 and 32 are also rejected under 35 USC § 103(a) as being obvious in view of the teachings of Davies, cited above. Claims 4 and 9 have been cancelled and thus the rejection of these claims are *moot*. For the reasons as provided *supra*, Applicants submit that the claimed invention is also not rendered obvious by the teachings of Davies. With regard to claims 24-30 and 32 the Examiner asserts that the claimed product or structure is substantially identical to that disclosed to Davies because it is made by a similar method of making such that it is obvious.

Davies does not teach or suggest stabilizing the calcium phosphate phases by doping the hydroxyapatite with exogenously added stabilizing entities. Davies nowhere teaches or suggests the chemical effect a quartz substrate would have, if any, on the thin film. Its sole contemplated use is to provide a suitable physical substrate that could be sintered and could be used in analytical testing. This is also further supported by the fact that Davies teaches the use of other materials such as metals, polymers or ceramics as a support. Davies teaching of the substrate is merely as a physical support. Davies only teaches a thin film as made on a substrate that has analytical use. Thus the Davies analytical film does not possess the characteristics of the claimed composition in that it cannot be used as an implant or bulk device.

Davies teachings do not contemplate implantable matrices comprising the presently claimed composition or bulk ceramic pieces. Davies in fact teaches away from the invention of stabilized calcium phosphate phases because Davies suggests using other materials for substrates such as ceramics and polymers that would not provide any type of stabilizing entity and also Davies only teaches thin films as supported on a substrate for analytical use only. Further, Davies does not suggest doping the hydroxyapatite with stabilizing entities and a method of intimate mixing for the stabilization to occur in order to create the claimed microporous and macroporous morphology of bulk and three-dimensional pieces. For these reasons, the presently claimed invention is not obvious in view of the Davies reference.

Conclusions

In summary, Applicants respectfully submit that the claimed invention is both novel and nonobvious and accordingly request withdrawal of the all rejections under 35 USC §§ 102(a) or (b) and USC § 103(a).

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner For Patents, Washington, DC 20231, on January 16, 2001.

Grace R. Rippy